Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study

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Lancet 2013; 382: 1646–54

Published Online July 22, 2013 http://dx.doi.org/10.1016/S0140-6736(13)60899-5

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Summary

Background Epilepsy is associated with high rates of premature mortality, but the contribution of psychiatric comorbidity is uncertain. We assessed the prevalence and risks of premature mortality from external causes such as suicide, accidents, and assaults in people with epilepsy with and without psychiatric comorbidity.

Methods We studied all individuals born in Sweden between 1954 and 2009 with inpatient and outpatient diagnoses of epilepsy (n=69 995) for risks and causes of premature mortality. Patients were compared with age-matched and sex-matched general population controls (n=660 869) and unaffected siblings (n=81 396). Sensitivity analyses were done to investigate whether these odds differed by sex, age, seizure types, comorbid psychiatric diagnosis, and different time periods after epilepsy diagnosis.

Findings 6155 (8.8%) people with epilepsy died during follow-up, at a median age of 34·5 (IQR 21·0–44·0) years with substantially elevated odds of premature mortality (adjusted odds ratio [aOR] of 11·1 [95% CI 10·6–11·6] compared with general population controls, and 11·4 [10·4–12·5] compared with unaffected siblings). Of those deaths, 15·8% (n=972) were from external causes, with high odds for non-vehicle accidents (aOR 5·5, 95 % CI 4·7–6·5) and suicide (3·7, 3·3–4·2). Of those who died from external causes, 75·2% had comorbid psychiatric disorders, with strong associations in individuals with co-occurring depression (13·0, 10·3–16·6) and substance misuse (22·4, 18·3–27·3), compared with patients with no epilepsy and no psychiatric comorbidity.

Interpretation Reducing premature mortality from external causes of death should be a priority in epilepsy management. Psychiatric comorbidity plays an important part in the premature mortality seen in epilepsy. The ability of health services and public health measures to prevent such deaths requires review.

Funding Wellcome Trust, the Swedish Prison and Probation Service, and the Swedish Research Council.

Introduction

Epilepsy accounts for an estimated 0·7% of the global burden of disease.[1] It affects around 70 million people,[2] and contributes to over 17 million disability-adjusted life-years annually.[1] Premature mortality is substantial[3] and almost half of epilepsy-related deaths occur in those younger than 55 years, corresponding to standardised mortality ratios above 10 for hospitalised patients.[4]

Suicide is associated with up to 5% of all epilepsy deaths,[5] but whether epilepsy is independently associated with suicide is unclear. One study suggested that epilepsy is an independent risk factor for suicide after controlling for psychiatric comorbidity,[6] but studies from Canada[7] and the UK[8] reported no independent relation. There have also been conflicting conclusions about whether epilepsy is a risk factor for suicide when psychiatric comorbidity is not present.[6,7] Clarification would assist national suicide prevention strategies that increasingly focus on high-risk populations,[9,10] particularly if such groups can be identified, and could also inform treatment guidelines.

Other major causes of epilepsy-related deaths are vehicle and non-vehicle accidents,[10,11] which contribute to up to 16% of deaths.[12] Restrictions for drivers with epilepsy have probably contributed to death rates from motor vehicle accidents not being significantly higher than that of the general population in certain countries.[7] However, the role of public health and education measures in reducing mortality from non-vehicle accidents in patients with epilepsy is uncertain. In particular, possible associations of non-vehicle accidental deaths with psychiatric disorders need clarification, and previous studies have not investigated psychiatric comorbidity.[11]

In our 41-year population study of 69 995 individuals with epilepsy, we aimed to investigate prevalence and risks of premature mortality, and to address two specific issues. First, whether epilepsy is independently associated with external causes of death. To clarify this, we compared people with epilepsy with the general population and unaffected sibling controls. If there is a link between epilepsy and death from external causes, the use of sibling controls enables clarification of whether this association is consistent with a causal hypothesis or due to residual confounding, including genetic and early environmental factors. Second, we investigated the association of epilepsy with premature mortality in patients with and without comorbid psychiatric disorders.

Methods

Study setting

We linked several longitudinal, nationwide population registers in Sweden: the Patient Register (held at the National Board of Health and Welfare), the Censuses

from 1970 and 1990 (Statistics Sweden), the Multi-Generation Register (Statistics Sweden), and the Cause-of-Death Register (National Board of Health and Welfare). The Multi-Generation Register connects every person born in Sweden from 1933 onwards and ever registered as living in Sweden after 1960 to their parents.[13] For immigrants, similar information exists for those who became citizens of Sweden before aged 18 years, together with one or both parents. In Sweden, all residents including immigrants have a unique ten-digit personal identification number that is used in all national registers, thus making the linking of data possible. We selected a cohort of people born between 1954 and 2009, and followed them up for up to 41 years, from 1969 to the end of follow-up in 2009 (n=7 238 800). The Patient Registers started in 1969; hence we began our follow-up at that point, which meant that children diagnosed with epilepsy who died between 1954 and 1968 were not included in the cohort. A sensitivity analysis addressed whether this affected the main findings. Using the Multi-Generation Register, we also identified patients with epilepsy who had full siblings without epilepsy.

The Regional Ethics Committee at Karolinska Institutet approved the study (2009/939-31/5). Data were merged and anonymised by an independent government agency (Statistics Sweden), and the code linking the personal identification numbers to the new case numbers was destroyed immediately after merging. Therefore, informed consent was not required.

Measures

Epilepsy

Epilepsy was identified through the National Patient Register, which includes individuals hospitalised (starting in 1969 but with total national coverage from 1987) or having outpatient appointments with specialist physicians (since 2001) in Sweden.[14] Patients with epilepsy had to have had at least one episode in which the diagnosis was made according to the International Classification of Diseases (ICD) ICD-8 (1969–1986; diagnostic codes 345.00–345.99), ICD-9 (1987–1996; codes 345J, K, L, M, N, P, Q, W, X), or ICD-10 (from 1997 onwards; codes G40.1–G40.9, G41).

Diagnostic validity

Swedish patient register data for diagnoses have good to excellent validity for a range of disorders, including neurological conditions such as acute stroke[15] and Guillain-Barré syndrome,[16] and psychiatric illnesses such as bipolar disorder[17] and schizophrenia.[18] Overall, the positive predictive value of the inpatient register, in a recent review, was found to be 85–95% for most diagnoses.[19] Less is known about comorbidity, although one study found fair to moderate agreement for comorbid substance misuse in schizophrenia (κ=0·37, standard error 0·23, p<0·001, corresponding to 68% full agreement).[20] Since only around 1% of hospital admissions have missing personal identification numbers,[21] the register has been used in various epidemiological investigations.[22,23]

Outcome measures

Data for causes of death were retrieved for all individuals who died between 1969 and 2009. The Cause of Death register, based on death certificates, covers over 99% of all deaths.[24] We extracted both all-cause mortality data and separately by ICD chapter, including external causes. Within external causes, we further examined deaths by suicide, vehicle and non-vehicle accidents, and assault. In line with previous work,[25] undetermined deaths (ICD codes Y10-Y34) were included as suicides since their exclusion would underestimate actual rates.[26]

Sociodemographic and psychiatric covariates

Mean lifetime disposable income (divided into thirds) was used as a proxy for income, and used as a dichotomous variable (lowest tertile *vs* top two tertiles). If this information was unavailable, family lifetime disposable income, or parents' lifetime disposable income was used instead and similarly divided into tertiles. Single marital status was defined as being unmarried at end of

	Patients with epilepsy (n=69 995)	General population controls (n=660 869)	Patients with epilepsy with unaffected siblings (n=48 437)	Unaffected sibling controls (n=81 396)
Male, n (%)	36 999 (52·9%)	348 561 (52·7%)	22 751 (53·0%)	41 786 (51·3%)
Single status, n (%)	50 099 (71·6%)	417 053 (63·1%)	36 257 (74·9%)	56 018 (68·8%)
Immigrant status, n (%)	1064 (1·5%)	20 125 (3·0%)	207 (0·4%)	438 (0·5%)
Lifetime individual mean disposable income, 1000 SEK (SD)	1041 (933)	1208 (1201)	1033 (1041)	1151 (1010)
Median age at diagnosis, years (IQR)	18·0 (7·9–31·5)	..	16·1 (7·2–28·7)	..
Median age at death, years (IQR)	34·5 (21·0–44·0)	38·9 (27·9–46·7)	31·7 (17·7–41·9)	36·2 (24·8–44·8)

Data for single status were not available for 1527 individuals with epilepsy and 12 259 matched population controls, 910 patients with epilepsy with sibling controls, and 301 unaffected sibling controls. Data for individual income were not available for 14 441 individuals with epilepsy, 139 580 matched population controls, 10 548 epilepsy patients with sibling controls, and 15 948 unaffected sibling controls. SEK=Swedish krona. IQR=interquartile range.

Table 1: **Baseline sociodemographic information for cohorts of individuals with epilepsy and comparison groups**

follow-up. Immigrant status was defined as being born outside of Sweden. Missing data were not replaced by imputation or other methods.

Any psychiatric, drug, and alcohol use disorders were defined using inpatient (1969–2009) and outpatient (2001–09) primary or secondary diagnoses of any psychiatric condition (ICD-8: 290–315; ICD-9: 290–319; ICD-10: F00–F99), alcohol or drug use or dependence (ICD-8: 303, 304; ICD-9: 303, 304, 305.1, 305.9; ICD-10: F10–F19, except x.5), and depression and related mood disorders (ICD-8: 296, 298.0, 300.4; ICD-9: 296, 298A, 300E, 311; ICD-10: F32–F39).

Analyses

For each patient, up to ten general population controls without any diagnosis of epilepsy were matched individually by birth year and sex (n=660 869). We estimated the association between having been diagnosed with epilepsy and causes of death, as per related work using matched or sibling controls,[20,23] using the clogit command in Stata, version 12 (StataCorp). The clogit command fits conditional (fixed effects) logistic regression models to matched case-control or cohort groups. We included three confounders (low income, single, and immigrant status) on theoretical grounds, based on related work in severe mental illness,[20,27] and also tested whether they were each independently associated with either case (epilepsy diagnosis) or control and outcome measures, respectively, in univariate analyses at the 5% level of significance.[28]

See Online for appendix

	Patients, n (%)	Controls, n (%)
Pre-existing diagnoses		
Any psychiatric diagnosis	12 631 (18·0%)	23 067 (3·5%)
Substance misuse	4764 (6·8%)	6403 (1·0%)
Alcohol	3743 (5·3%)	4512 (0·7%)
Other substances	2449 (3·5%)	2933 (0·4%)
Depression	2377 (3·4%)	5390 (0·8%)
New diagnoses		
Any psychiatric diagnosis	15 856 (22·7%)	45 314 (6·9%)
Substance misuse	3305 (4·7%)	12 543 (1·9%)
Alcohol	2496 (3·6%)	9008 (1·4%)
Other substances	2016 (2·9%)	5668 (0·9%)
Depression	3821 (5·5%)	16 523 (2·5%)
Lifetime diagnoses		
Any psychiatric diagnosis	28 487 (40·7%)	68 381 (10·3%)
Substance misuse	8069 (11·5%)	18 946 (2·9%)
Alcohol	6239 (8·9%)	13 520 (2·0%)
Other substances	4465 (6·4%)	8601 (1·3%)
Depression	6198 (8·9%)	21 913 (3·3%)

Data are number (%) with psychiatric comorbidity. Any psychiatric disorder includes substance use diagnoses. New diagnoses refer to any psychiatric diagnoses made after first epilepsy diagnosis.

Table 2: **Prevalence of pre-existing, new, and lifetime psychiatric morbidity in individuals with epilepsy**

Sibling control studies

To account for possible familial confounding, we did additional analyses that used unaffected full siblings of patients as controls. In this analysis, we identified as cases those individuals with epilepsy who also had full siblings without epilepsy, and these individuals were compared with their unaffected full siblings (n=81 396) using matched conditional logistic regression, and analyses were adjusted for age and sex.

Sensitivity analyses

We also did the following subanalyses. First, we investigated categories of epilepsy and classified them into four types according to the diagnosis at first admission: complex partial seizures (ICD-8: 345.31; ICD-9: 345M, 345N; ICD-10: G40.2), other partial seizures (ICD-8: 345.30, 345.38, 345.39; ICD-10: G40.0, G40.1), generalised epilepsy (ICD-8: 345.00, 345.09, 345.10, 345.11; ICD-9: 345J, 345K; ICD-10: G40.3), and other or unspecified epilepsy (ICD-8: 345.18, 345.19, 345.20, 345.29, 345.32, 345.33, 345.9; ICD-9: 345L, 345P, 345Q, 345W, 345X; ICD-10: G40.4, G40.5, G40.6, G40.7, G40.8, G40.9, G41).[23] Second, based on International League Against Epilepsy recommendations of subclassifying epilepsy into clinical syndromes,[29] we undertook a further sensitivity analysis based solely on ICD-10 codes, based on work using Danish national registers.[30] Third, as an index of severity, we compared individuals whose first hospital treatment episode lasted for 9 days or more (90th percentile) with the others (inpatients and outpatients). Fourth, we investigated differences by diagnostic threshold by comparing individuals with one or more diagnoses of epilepsy with those with two or more diagnoses. Fifth, we compared individuals with epilepsy by birth order. Finally, deaths by 10-year age-bands were investigated, and we also compared mortality risks in children who died under the age of 15 years with other ages. We followed STROBE guidelines (appendix).

Results

We identified 69 995 individuals with epilepsy and compared them with 660 869 age-matched and sex-matched controls (table 1). Patients were followed up for an average of 9 years (interquartile range [IQR] 5–18 years). Rates of psychiatric comorbidity were 18·0% before diagnosis of epilepsy and 22·7% after diagnosis, with high rates of depression and substance misuse (drug and alcohol use disorders; table 2).

6155 (8·8%) patients with epilepsy died before the end of the follow-up period compared with 4892 (0·7%) controls. We found a substantially elevated increased odds for all-cause mortality in individuals with epilepsy after matching for age and sex (odds ratio 14·1, 95% CI 13·5–14·7), and after adjustment for sociodemographic confounders (adjusted odds ratio [aOR] 11·1, 95% CI 10·6–11·6). In men, 3786 (10·2%) patients died during follow-up, compared with 3322 (1·0%) controls

(aOR 10·1, 95% CI 9·5–10·7); in women, 2369 (7·2%) patients died, compared with 1570 (0·5%) controls (13·0, 12·0–14·0). Adjusted odds ratios for ICD subcategories of mortality were mostly elevated (table 3), with most deaths in patients with diseases caused by the same underlying disease process as that leading to epilepsy. Of these, neoplasms (23·0% of deaths; aOR 11·2, 95% CI 10·3–12·2), and diseases of the nervous system (21·3% of deaths; 71, 57–88) were the two major causes. The next largest category was external causes (15·8% of deaths). The highest mortality odds ratio was for conditions originating in the perinatal period (1·6% of deaths; aOR 126, 95% CI 46–348).

The odds for external causes of death in individuals with epilepsy were also elevated (aOR 3·6, 95% CI 3·3–4·0; table 4). For suicide (n=510), the adjusted odds ratio was 3·7 (95% CI 3·3–4·2). Deaths caused by non-vehicle accidents (n=362) had the highest odds of death (aOR 5·5, 95% CI 4·7–6·5) among external causes (table 4). For death by assault (n=30), the adjusted odds ratio was 2·8 (95% CI 1·6–4·8). In further analyses of non-vehicle accidents, we found 135 deaths (37·3% of non-vehicle accidents) due to accidental drug poisoning, 60 (16·6%) due to accidental falls, 55 (15·2%) drowning, and 112 (30·9%) other and unspecified accidental deaths.

We compared patients with epilepsy (n=48 437) with their unaffected siblings (n=81 396) for all-cause mortality, natural causes, and specific external causes. All risk estimates remained raised, including those for suicide (aOR 2·9, 95% CI 2·4–3·6) and non-vehicle accidents (6·3, 4·6–8·8; table 4). We found no evidence of familial confounding for non-vehicle accidents (since risk estimates were significant and of the same magnitude as with the population controls).

Differences in mortality due to any external cause did not vary by severity and diagnostic thresholds in sensitivity analyses (table 5). Although odds of death by external causes were lower in those with two or more diagnoses of epilepsy, this difference was not significant, and confidence intervals overlapped. We found some evidence for differences by epilepsy types in odds of external cause mortality. Special epilepsy syndromes (ICD-10 G40.5, including G40.5L epileptic encephalopathy with continuous spike-and-wave during sleep) had higher odds of non-vehicle accidents (aOR 24·2, 95% CI 9·2–63·9) than other types of epilepsy (table 5). For suicide, women had higher odds of death (aOR 5·0, 95% CI 4·0–6·3) than men (3·3, 2·8–3·8; interaction test p=0·002). After stratification by age groups, we found some evidence of higher odds ratios of external causes of mortality with increasing age. We found no differences in odds or prevalence of mortality by birth order. Odds ratios of external causes were higher in the first 6 months after diagnosis of epilepsy (table 5). Sensitivity analyses for all natural causes of death, and specifically for neoplasms and neurological causes, are shown in the appendix.

	Deaths in patients n (% of deaths)	Deaths in controls n (% of deaths)	Adjusted odds ratio (95% CI)
I Certain infectious and parasitic diseases	98 (1·6%)	68 (1·4%)	10·6 (7·3–15·4)
II Neoplasms	1416 (23·0%)	1146 (23·4%)	11·2 (10·3–12·2)
III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	19 (0·3%)	18 (0·4%)	15·3 (6·7–34·9)
IV Endocrine nutritional and metabolic diseases	277 (4·5%)	151 (3·1%)	14·2 (11·3–17·9)
V Mental and behavioural disorders	274 (4·5%)	122 (2·5%)	15·9 (12·1–20·8)
VI Diseases of the nervous system	1309 (21·3%)	124 (2·5%)	71·1 (57·3–88·4)
IX Diseases of the circulatory system	541 (8·8%)	655 (13·4%)	6·4 (5·6–7·3)
X Diseases of the respiratory system	281 (4·6%)	81 (1·7%)	21·2 (15·6–28·8)
XI Diseases of the digestive system	241 (3·9%)	149 (3·0%)	11·8 (9·3–14·9)
XIII Diseases of the musculoskeletal system and connective tissue	30 (0·5%)	19 (0·4%)	11·1 (5·5–22·4)
XIV Diseases of the genitourinary system	39 (0·6%)	15 (0·3%)	14·2 (7·0–28·7)
XVI Certain conditions originating in the perinatal period	96 (1·6%)	8 (0·2%)	126·3 (45·9–347·6)
XVII Congenital malformations, deformations, and chromosomal abnormalities	449 (7·3%)	94 (1·9%)	38·1 (27·7–52·5)
XVIII Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	106 (1·7%)	134 (2·7%)	7·2 (5·3–9·8)
Other non-external (chapters VII, VIII, XII, XV, XIX)	7 (0·1%)	7 (0·2%)	12·7 (3·0–52·8)
XX External causes of morbidity and mortality	972 (15·8%)	2101 (42·9%)	3·6 (3·3–4·0)
Total deaths	6155 (100%)	4892 (100%)	11·1 (10·6–11·6)

Adjusted odds ratios refer to the odds of premature death by ICD chapter in patients with epilepsy compared with controls matched by sex and birth year, and adjusted by income, and immigrant and single status.

Table 3: **Prevalence and odds of premature mortality in epilepsy, by International Classification of Diseases chapter**

	Odds ratio for death compared with population controls (aOR [95% CI])	Odds ratio for death compared with unaffected sibling controls (aOR [95% CI])
All-cause mortality	11·1 (10·6–11·6)	11·4 (10·4–12·5)
Natural causes	15·5 (14·6–16·4)	16·7 (14·9–18·7)
Neoplasms	11·2 (10·3–12·2)	11·3 (9·4–13·7)
Nervous system	71·1 (57·3–88·4)	86·9 (54·3–139·1)
External causes	3·6 (3·3–4·0)	3·2 (2·7–3·7)
Suicide	3·7 (3·3–4·2)	2·9 (2·4–3·6)
All accidents	3·6 (3·1–4·1)	3·6 (2·9–4·5)
Vehicle	1·4 (1·1–1·8)	1·5 (1·1–2·2)
Other	5·5 (4·7–6·5)	6·3 (4·6–8·8)
Drug poisoning	5·1 (3·9–6·5)	5·7 (3·3–9·7)
Fall	8·5 (5·3–13·7)	10·0 (2·9–33·8)
Drowning	7·7 (4·7–12·7)	9·5 (3·5–25·7)
Other and unspecified	4·9 (3·6–6·5)	5·2 (3·2–8·5)
Assault	2·8 (1·6–4·8)	1·7 (0·9–3·3)

Data are adjusted odds ratios (aOR) of external deaths compared with population controls (matched for age and sex, and adjusted for income, and marital and immigration status) or unaffected sibling controls (adjusted for age and sex).

Table 4: **Risks of premature death in individuals with epilepsy compared to population controls and unaffected siblings**

There was an increased prevalence of psychiatric disorders in epilepsy patients, and specifically for alcohol and drug use disorders, and depression (table 2). By epilepsy syndrome, special syndromes had higher comorbidity (81·3%) than unspecified (45·2%), focal (36·0%), generalised (29·6%) and other groups. Of those who died from external causes during follow-up, 75% (731 of 972; aOR 10·6, 95% CI 9·2–12·2) had a lifetime psychiatric diagnosis (including substance misuse) and, specifically, 549 (56%; 22·4, 18·3–27·3) had a history of substance

	External causes		Suicide or uncertain		Vehicle accidents		Other accidents	
	n (% deaths)	aOR (95% CI)	n (% deaths)	aOR (95% CI)	n (% deaths)	aOR (95% CI)	n (% deaths)	aOR (95% CI)
No epilepsy (n=660 869)	2101 (42·9%)	1·0 (ref)	1058 (21·6%)	1·0 (ref)	517 (10·6%)	1·0 (ref)	453 (9·3%)	1·0 (ref)
Epilepsy								
Sex								
Male (n=36 999)	711 (18·8%)	3·4 (3·1–3·8)	346 (9·1%)	3·3 (2·8–3·8)	74 (2·0%)	1·5 (1·1–2·0)	281 (7·4%)	5·2 (4·3–6·3)
Female (n=32 996)	261 (11·0%)	4·3 (3·6–5·1)	164 (6·9%)	5·0 (4·0–6·3)	17 (0·7%)	1·1 (0·6–2·1)	81 (3·4%)	7·2 (5·1–10·3)
Threshold								
≥1 diagnosis (n=69 995)	972 (15·8%)	3·6 (3·3–4·0)	510 (8·3%)	3·7 (3·3–4·2)	91 (1·5%)	1·4 (1·1–1·8)	362 (5·9%)	5·5 (4·7–6·5)
≥2 diagnoses (n=48 105)	535 (12·9%)	3·1 (2·8–3·5)	257 (6·2%)	2·8 (2·4–3·4)	55 (1·3%)	1·5 (1·0–2·0)	218 (5·2%)	5·5 (4·5–6·8)
Severity								
Less severe (n=62 143)	802 (17·4%)	3·6 (3·3–4·0)	428 (9·3%)	3·9 (3·4–4·4)	77 (1·7%)	1·6 (1·2–2·1)	293 (6·4%)	5·1 (4·2–6·0)
More severe (n=7852)	170 (11·0%)	3·4 (2·7–4·4)	82 (5·3%)	2·7 (1·9–3·8)	14 (0·9%)	0·8 (0·4–1·8)	69 (4·5%)	9·3 (6·0–14·5)
Source								
Inpatient (n=50 071)	887 (15·2%)	3·7 (3·3–4·1)	459 (7·9%)	3·7 (3·2–4·2)	85 (1·5%)	1·5 (1·1–1·9)	334 (5·7%)	5·7 (4·8–6·8)
Outpatient only (n=19 924)	85 (25·3%)	3·1 (2·4–4·1)	51 (15·2%)	3·8 (2·7–5·4)	6 (1·8%)	1·0 (0·4–2·4)	28 (8·3%)	4·2 (2·6–7·0)
Type of seizures*								
Complex partial (n=8382)	56 (13·0%)	2·2 (1·6–3·1)	31 (7·2%)	2·9 (1·8–4·5)	6 (1·4%)	1·2 (0·5–3·1)	20 (4·6%)	2·6 (1·4–4·8)
Other partial (n=5857)	55 (15·1%)	1·9 (1·3–2·8)	33 (9·0%)	1·9 (1·1–3·2)	8 (2·2%)	1·4 (0·6–3·3)	15 (4·1%)	3·1 (1·4–6·6)
Generalised (n=15 315)	179 (12·3%)	1·8 (1·5–2·3)	87 (6·0%)	1·8 (1·4–2·5)	20 (1·4%)	0·9 (0·5–1·6)	69 (4·7%)	3·1 (2·1–4·6)
Other and unspecified (n=40 441)	682 (17·5%)	5·1 (4·5–5·7)	359 (9·2%)	5·1 (4·4–6·0)	57 (1·5%)	1·7 (1·2–2·5)	258 (6·6%)	7·3 (6·0–8·9)
Type of epilepsy†								
Focal (n=12 841)	55 (9·0%)	1·5 (1·1–2·1)	31 (5·1%)	2·0 (1·3–3·0)	7 (1·1%)	0·7 (0·3–1·7)	19 (3·1%)	2·0 (1·1–3·6)
Generalised (n=7593)	24 (14·1%)	1·4 (0·9–2·3)	12 (7·1%)	1·8 (0·9–3·5)	3 (1·8%)	0·5 (0·2–1·8)	9 (5·3%)	2·6 (1·1–6·0)
Encephalopathy and mixed (n=1894)	10 (4·9%)	2·5 (1·2–5·5)	7 (3·4%)	4·1 (1·5–10·8)	1 (0·5%)	1·0 (0·1–8·8)	2 (1·0%)	1·8 (0·3–9·9)
Special syndromes (n=894)	39 (26·4%)	9·5 (5·3–17·0)	16 (10·8%)	4·3 (2·0–9·3)	1 (0·7%)	2·7 (0·2–31·2)	22 (14·9%)	24·2 (9·2–63·9)
Other epilepsy (n=710)	8 (14·8%)	5·4 (2·1–14·4)	0 (0·0%)	..	1 (1·9%)	1·8 (0·1–24·2)	7 (13·0%)	12·8 (3·9–42·6)
Unspecified epilepsy (n=29 997)	352 (16·1%)	4·8 (4·1–5·5)	173 (7·9%)	4·3 (3·5–5·3)	31 (1·4%)	2·3 (1·5–3·6)	139 (6·3%)	6·9 (5·4–8·8)
Age at death								
0–15 (n=69 995)	45 (4·0%)	3·8 (1·9–7·6)	7 (0·6%)	4·7 (1·0–22·2)	5 (0·4%)	..	27 (2·4%)	5·1 (2·2–11·6)
16–25 (n=68 877)	135 (14·8%)	1·8 (1·3–2·3)	67 (7·3%)	1·9 (1·3–2·8)	20 (2·2%)	0·8 (0·4–1·5)	40 (4·4%)	3·4 (2·0–5·6)
26–35 (n=67 963)	276 (21·8%)	3·3 (2·8–4·0)	157 (12·4%)	3·3 (2·6–4·3)	28 (2·2%)	1·7 (1·1–2·8)	95 (7·5%)	5·3 (3·7–7·4)
36–45 (n=66 691)	338 (20·7%)	4·9 (4·2–5·7)	189 (11·6%)	5·1 (4·2–6·3)	20 (1·2%)	1·6 (0·9–2·6)	135 (8·3%)	7·0 (5·4–9·1)
46–56 (n=65 055)	178 (14·6%)	5·7 (4·7–7·0)	90 (7·4%)	5·5 (4·2–7·3)	18 (1·5%)	6·3 (3·3–12·0)	65 (5·3%)	6·3 (4·4–9·0)
Birth order								
Firstborn (n=21 131)	263 (14·3%)	3·1 (2·7–3·7)	129 (7·0%)	3·2 (2·5–4·1)	28 (1·5%)	1·2 (0·8–2·0)	107 (5·8%)	5·2 (3·8–7·0)
Not firstborn (n=27 306)	314 (15·3%)	3·6 (3·1–4·2)	169 (8·2%)	4·0 (3·2–4·9)	36 (1·8%)	1·6 (1·0–2·4)	102 (5·0%)	4·7 (3·5–6·2)
No siblings (n=21 558)	395 (17·4%)	4·0 (3·4–4·7)	212 (9·4%)	3·7 (3·0–4·6)	27 (1·2%)	1·4 (0·9–2·4)	153 (6·8%)	6·6 (5·1–8·7)
Time period								
0–182 days (n=69 995)	97 (10·8%)	13·8 (9·2–20·9)	50 (5·6%)	17·9 (9·8–32·6)	7 (0·8%)	3·6 (1·0–12·5)	39 (4·4%)	23·5 (10·3–53·4)
183–365 days (n=69 096)	58 (11·5%)	8·3 (5·3–12·9)	36 (7·1%)	13·0 (6·9–24·3)	6 (1·2%)	2·1 (0·6–7·1)	15 (3·0%)	10·6 (4·0–28·1)
≥366 days (n=68 592)	817 (17·2%)	3·3 (3·0–3·6)	424 (8·9%)	3·3 (2·9–3·8)	78 (1·6%)	1·4 (1·0–1·8)	308 (6·5%)	5·2 (4·4–6·2)

% deaths refers to proportion of all deaths for row category which were due to the column cause (eg, of the male deaths in epilepsy, 18·8% were from external causes). Adjusted odds ratios (aOR) report odds of mortality in individuals with epilepsy compared with general population controls (matched for age and sex, and adjusted for income, and marital and immigration statuses). Suicide category includes undetermined deaths.*Complex partial (ICD-8: 345.31; ICD-9: 345M, 345N; ICD-10: G40.2); other partial (ICD-8: 345.30, 345.38, 345.39; ICD-10: G40.0, G40.1); generalised (ICD-8: 345.00, 345.09, 345.10, 345.11; ICD-9: 345J, 345K; ICD-10: G40.3); other and unspecified (ICD-8: 345.18, 345.19, 345.20, 345.29, 345.32, 345.33, 345.9; ICD-9: 345L, 345P, 345Q, 345W, 345X; ICD-10: G40.4, G40.5, G40.6, G40.7, G40.8, G40.9, G41). †Focal (ICD-10: G40.0, G40.1, G40.2); generalised (ICD-10: G40.3); encephalopathy and mixed (ICD-10: G40.4); special syndromes (ICD-10: G40.5); other epilepsy (ICD-10: G40.8); unspecified epilepsy (ICD-10: G40.6, G40.7, G40.9).

Table 5: **Mortality risks after diagnosis with epilepsy, stratified by diagnostic threshold, sex, severity, patient type, epilepsy subtype, age group, birth order, and time after first diagnosis**

	External causes		Suicide or uncertain		Vehicle accidents		Other accidents	
	n (%)	aOR (95% CI)	n (%)	aOR (95% CI)	n (%)	aOR (95% CI)	n (%)	aOR (95% CI)
Any psychiatric disorder								
No epilepsy, no psychiatric disorder	1230 (0·2%)	1·0 (ref)	488 (0·1%)	1·0 (ref)	452 (0·1%)	1·0 (ref)	234 (0·1%)	1·0 (ref)
No epilepsy, psychiatric disorder	871 (1·3%)	5·8 (5·2–6·6)	570 (0·8%)	9·3 (7·8–11·0)	65 (0·1%)	1·0 (0·7–1·4)	219 (0·3%)	7·5 (5·9–9·6)
Epilepsy, no psychiatric disorder	241 (0·6%)	2·3 (1·9–2·8)	81 (0·2%)	2·1 (1·5–2·9)	61 (0·1%)	1·9 (1·3–2·6)	91 (0·2%)	3·5 (2·5–4·9)
Epilepsy, psychiatric disorder	731 (2·6%)	10·6 (9·2–12·2)	429 (1·5%)	14·0 (11·5–17·0)	30 (0·1%)	0·9 (0·6–1·5)	271 (1·0%)	23·3 (17·4–31·3)
Depression								
No epilepsy, no depression	1790 (0·3%)	1·0 (ref)	809 (0·1%)	1·0 (ref)	500 (0·1%)	1·0 (ref)	411 (0·1%)	1·0 (ref)
No epilepsy, depression	311 (1·4%)	5·1 (4·3–6·1)	249 (1·1%)	9·9 (7·9–12·4)	17 (0·1%)	1·1 (0·6–1·9)	42 (0·2%)	2·3 (1·5–3·4)
Epilepsy, no depression	745 (1·2%)	3·3 (3·0–3·7)	328 (0·5%)	3·1 (2·6–3·6)	86 (0·1%)	1·4 (1·1–1·9)	316 (0·5%)	5·5 (4·6–6·6)
Epilepsy, depression	227 (3·7%)	13·0 (10·3–16·6)	182 (2·9%)	22·9 (16·6–31·6)	5 (0·1%)	1·1 (0·4–2·9)	46 (0·7%)	9·9 (6·1–16·1)
Substance misuse								
No epilepsy, no substance misuse	1562 (0·2%)	1·0 (ref)	759 (0·1%)	1·0 (ref)	477 (0·1%)	1·0 (ref)	263 (0·1%)	1·0 (ref)
No epilepsy, substance misuse	539 (2·8%)	8·6 (7·4–10·0)	299 (1·6%)	9·4 (7·6–11·6)	40 (0·2%)	1·7 (1·1–2·5)	190 (1·0%)	20·0 (14·3–27·9)
Epilepsy, no substance misuse	423 (0·7%)	2·2 (1·9–2·6)	191 (0·3%)	2·2 (1·8–2·6)	68 (0·1%)	1·2 (0·9–1·7)	151 (0·2%)	4·2 (3·2–5·4)
Epilepsy, substance misuse	549 (6·8%)	22·4 (18·3–27·3)	319 (4·0%)	21·5 (16·6–27·8)	23 (0·3%)	3·1 (1·7–5·5)	211 (2·6%)	43·3 (28·8–65·1)

Number of deaths in epilepsy and associated controls, stratified by psychiatric diagnoses. % is percentage of deaths from a particular cause within the row sample (eg, of those with no epilepsy and no psychiatric disorder, 0·2% died from external causes). Adjusted odds ratios (aOR) report odds of morality compared with the reference group. Suicide category includes undetermined deaths.

Table 6: **Associations of external causes of death in epilepsy with psychiatric comorbidity**

misuse, and 227 (23%; aOR 13·0, 95% CI 10·3–16·6) had depression (table 6). We found no differences in odds of mortality between psychiatric disorders diagnosed before epilepsy and those diagnosed after (data not shown). In those with psychiatric comorbidity, we found evidence for an association between epilepsy and external cause mortality (aOR 2·3, 95% CI 1·9–2·8), suicide (2·1, 1·5–2·9), vehicle accidents (1·9, 1·3–2·6), and non-vehicle accidents (aOR 3·5, 2·5–4·9). In addition, we looked at all natural causes of death, and the two most common causes (neoplasms, neurological) and did not find strong associations with psychiatric comorbidity (appendix).

Discussion

Our results indicate high rates of premature mortality in epilepsy, and highlight the substantial contribution of psychiatric comorbidity to this mortality. The findings potentially contribute to the clinical management of epilepsy for neurology, psychiatry, and primary care services by presenting information on associations with treatable psychiatric disorders. To our knowledge, this is the first time that unaffected sibling controls have been used to assess mortality in epilepsy (panel).

We report three main findings. First, the adjusted odds of all-cause mortality, which followed individuals with epilepsy until they were 56 years old, was 11 compared with both general population and unaffected sibling controls. 16% of all epilepsy deaths were from external causes, which was the largest category of deaths that was not clearly related to underlying disease processes (such as brain tumours and infections). A notable finding was the high risk of death from non-vehicle accidents, with adjusted odds of death at 5·5 (95% CI 4·7–6·5). Second, we found evidence that epilepsy is an independent risk factor for all-cause and external causes of death. This was most clearly shown when we compared patients with their unaffected siblings. For external causes, the odds of mortality in people with epilepsy were increased at 2·9 for suicide and 3·6 for accidents compared with unaffected siblings.

The independent effect of epilepsy on suicide contrasts with some previous research,[7,8] but supports another population study,[6] which found an independent effect of epilepsy on external causes of death. We believe our findings are robust, since our study benefited from a large sample size, various sensitivity analyses, and examined familial confounding. Third, patients with epilepsy and psychiatric comorbidity have very high mortality. Specifically, individuals with epilepsy and comorbid depression had an odds ratio for suicide of 23 compared

with non-depressed general population controls, and those with epilepsy and comorbid substance misuse of 21. The corresponding odds of suicide in general population controls with depression but without epilepsy was 10. For deaths from non-vehicle accidents, there was a strong association with substance misuse (as suggested by an increase in odds of mortality of 43 in epilepsy and comorbid substance misuse, compared with 20 in general population controls without epilepsy but with substance misuse).

The high odds associated with congenital conditions and those arising in the perinatal period, such as cerebral palsy, is not surprising, since these underlying conditions are associated with the most severe forms of epilepsy. This mortality risk underlines the importance of preventing these causes of death during the perinatal period and perhaps the need to examine interventions to prevent epileptogenesis in those exposed to perinatal events.

Our finding of an 11-fold increase in odds of all-cause mortality compared with general population controls is higher than that reported in some other mortality studies, but consistent with the few studies that have examined premature mortality. For example, one population study in Sweden found standardised mortality ratios between 10 and 14 in hospitalised patients aged 15–54 years.[4] Furthermore, we reported an increased odds of suicide of 3·7 that is within the range reported in a recent systematic review.[5] Although a few population based studies have presented data for psychiatric comorbidity, estimates in our study are within the range of 19–48% reported in a review article,[31] and consistent with the 36% found in a community survey of patients with epilepsy.[32] Additionally, our prevalence of depression of 8·9% is similar to the 9·6% found in a recent study of 7403 individuals with epilepsy in England.[33]

***Panel:* Research in context**

Systematic review

We searched Medline for articles comparing mortality in epilepsy to general population controls and examining the role of psychiatric comorbidity, published up to March 29, 2013, with no language or date restrictions, and with the search terms "epilepsy" and ("mortality" or "death") and "psych*". We also scanned references of key articles. We identified two population-based case-control studies. A Danish study[6] (n=492 suicides) found epilepsy to be a risk factor for suicide independent of increased risk of psychiatric comorbidity. A Canadian study[7] (n=203 fatal and non-fatal accidents, suicide and suicide attempts, and self-inflicted injuries), however, found no increased risk of external causes of death in epilepsy after adjusting for comorbidity.

Interpretation

Our study substantially increases the evidence on the contribution of psychiatric morbidity to mortality in epilepsy. Additionally, for the first time, we examine odds of premature death in individuals with epilepsy compared with their unaffected siblings, and find that they do not differ significantly from mortality odds in epilepsy compared with general population controls. This strongly suggests that epilepsy is an independent risk factor for all-cause and external cause mortality. External causes of death were strongly associated with psychiatric conditions, and we conclude that premature mortality in epilepsy might be reduced with improved identification and treatment of these comorbidities.

Our findings suggest that risks for external causes of death, and potential treatments to mitigate these risks, need to be considered in patients with epilepsy. The importance of identifying, monitoring, and treating psychiatric comorbidity, discussed recently in an expert review,[34] is underscored by these results. This was most clearly shown in our finding that around three-quarters of deaths from external causes in the epilepsy cohort were in patients who had a lifetime psychiatric diagnosis. In particular, patients with psychiatric comorbidity in the period immediately after the first diagnosis of epilepsy represent a high-risk population that might benefit from closer monitoring, consultation with liaison psychiatry, and more intensive treatments. But our results also highlight the role of other risk factors beyond psychiatric comorbidity as suicide and accident deaths were increased in those without lifetime co-occurring psychiatric disorders. Such risk factors may include more sensitive measures of disease course and severity than we were able to investigate, treatment-related factors,[5] and direct effects of the condition on decision making in some people.[35] Additionally, the importance of other causes of death is also underlined by our findings; neurological causes had the highest rates and risks, and the contribution of sudden unexplained deaths needs further examination.[36]

Moreover, our findings highlight the importance of non-vehicle accidents as a major preventable cause of death in people with epilepsy. One possible implication is whether specific warnings and patient education, besides those already given, should be provided to patients about risks of non-vehicle accidents, including their link to substance misuse.

Although the relative risks were high, absolute rates of premature mortality from external causes were 1·4%, and any changes to clinical practice need to consider how to identify high-risk populations with low false positive rates. Nevertheless, as we found around a third of epilepsy patients had a comorbid psychiatric diagnosis, and around a tenth had comorbid substance misuse, clinical epilepsy services could review their liaison with psychiatric[37] and addiction services. The importance of substance misuse in suicide mortality was at least as important as depression, but it has not been highlighted in recent reviews.[34] Previous work has examined the role of alcohol comorbidity in suicide risk,[6] but little is known about comorbid drug use.

There are two main limitations in this study. The first is that we restricted our cohort to those born between 1954 and 2009. This was done to focus on premature mortality and so that our findings would not be potentially diluted by the large mortality effects of older people. This restriction also avoided cohort effects with older people, for whom services and treatments were considerably different before 1970. Nevertheless, results are confined to premature deaths. A second limitation is that we used patient registers to identify people with epilepsy, since it

was necessary to use routinely collected data to provide precision for the fairly rare outcomes investigated.

Syndromal approaches are now recommended to subclassify epilepsy[29] and translating ICD codes into these syndromes might be subject to some misclassification.[30] Nevertheless, using either ICD codes or syndromes, epilepsies that were not focal or generalised (and described variously as other or special epileptic syndromes) could incur higher risk of premature mortality. We used both outpatient and inpatient data to identify cases, and found no obvious differences in mortality. However, we might be missing a proportion of patients who never present to secondary services, although we estimate that this number would be small for a chronic illness such as epilepsy in a country with a comprehensive tax-funded health system such as Sweden, and over an average follow-up of 9 years. This small missing proportion is likely due to the long-standing practice for first diagnoses of epilepsy to be confirmed by specialist services.[38] Nevertheless, undersampling of patients with less severe symptoms could lead to an overestimation of the association with premature death if individuals with less severe disease are both less likely to be diagnosed and have fewer comorbidities and mortality risks.

We also only studied one country, and the generalisability to other countries is uncertain. An estimate of the prevalence of epilepsy based on our sample is difficult, since the 41 year cohort does not lend itself to such a calculation. However, when extrapolating the prevalence reported in this cohort to a lifetime prevalence, we find a similar prevalence estimate to that reported in other high-income countries.[2] Sweden is not dissimilar to other western European countries in suicide rates[39] but comparative information on death by accidents is limited. Finally, some of the causes of death may be prone to misclassification. Suicide and deaths from undetermined causes were combined to account for this, but it is possible that some accidental deaths are in fact suicides.[40]

Some accidental deaths will also be a direct consequence of seizures, and therefore the associations with substance misuse might not be causal. Treatment trials in this population are necessary to determine the precise role of substance misuse and other psychiatric disorders on premature death. We were also unable to examine the effect of psychiatric comorbidity on sudden unexpected deaths in epilepsy which contribute to around 4% of deaths in community samples,[41] and are defined as death due to sudden and unexplained respiratory failure or cardiac arrest.[36] Future research should examine the relation between epilepsy, psychiatric comorbidity, and prescribed medication (particularly selective serotonin reuptake inhibitors)[42] on sudden unexpected deaths. However, we did examine the association of psychiatric morbidity with two main causes of natural deaths, namely cancer and neurological diseases (appendix). We did not find strong associations with psychiatric comorbidity, which was not surprising since these underlying causes of epilepsy are likely to cause death directly.

We found no evidence of familial confounding in all-cause and external mortality, a somewhat unexpected finding, as previous studies have suggested that familial (genetic or early environmental) effects explain a substantial part of the association between epilepsy and violent crime.[23] However, it strengthens the hypothesis that epilepsy is on the causal pathway to premature death.

In summary, psychiatric comorbidity has an important role in the premature mortality seen in epilepsy. Reducing premature mortality from external causes of death should be a priority in epilepsy management. The ability of health services to prevent such deaths requires review.

Contributors

SF, PL, and CRN conceived and designed the study. AW analysed the data. SF drafted the report. All authors revised drafts and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This study was funded by Wellcome Trust (095806), the Swedish Prison and Probation Service, and the Swedish Research Council. We thank Marcus Boman, Karolinska Institutet, for assistance with data extraction and linkage.

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